See related Commentary on pages v and vi

Genetic Basis of Male Pattern Baldness

To the Editor:

Common pattern baldness (androgenetic alopecia) is the most common form of hair loss in humans. In Caucasians, normal male hair loss, commonly known as "male pattern baldness" (MPB; MIM 109200), is noticeable in about 20% of men aged 20, and increases steadily with age, so that a male in his 90s has a 90% chance of having some degree of MPB. In addition to being among the most common natural conditions that make men self-conscious, recent studies indicate associations of MPB with: (1) benign prostatic hyperplasia (MIM 600082; odds ratio (OR) = 3.23; 95% confidence interval (CI): 1.81–5.79) (Hawk *et al*, 2000); (2) coronary heart disease (relative risk = 1.36; 95% CI: 1.11–1.67) (Lotufo *et al*, 2000); (3) hyperinsulinemia (OR = 1.91; 95% CI: 1.02–3.56); and (4) insulin-resistance-associated disorders, such as obesity (MIM 601665; OR = 2.90; 95% CI: 1.76–4.79), hypertension (MIM 145500; OR = 2.09; 95% CI: 1.14–3.82), and dyslipidemia (OR = 4.45; 95% CI: 1.74–11.34) (Matilainen *et al*, 2000). MBP is also a risk factor for clinical prostate cancer (MIM 176807; relative risk = 1.50; 95% CI: 1.12–2.00) (Oh *et al*, 1998). Although it is a widely accepted opinion that common baldness is an autosomal dominant phenotype in men and an autosomal recessive phenotype in women, or indeed that baldness is genetically influenced, it is based on surprisingly little empirical data. Here we grade MBP, in 476 monozygotic (MZ) and 408 dizygotic (DZ) male twin pairs aged between 25 and 36 y and find a heritability of 0.81 (95% CI: 0.77–0.85), thus confirming that genetic effects play a major part in the progression of common hair loss.

Measures of hair loss were obtained in the course of an extensive semistructured telephone interview with respondent booklet, designed to assess physical, psychologic, and social manifestations of alcoholism and related disorders, conducted with 6265 twins born 1964 to 1971 from the volunteer-based Australian Twin Registry. All males (45% of the sample) were asked to rate their degree of hair loss, if any, using the Hamilton–Norwood Baldness scale (Norwood, 1975) (a standard classification scheme shown to have good test–retest reliability) (Hamilton, 1951; Norwood, 1975), which was printed in the respondent booklet (**Fig 1**). This data collection scheme was validated in a study by Ellis *et al* (1998), which compared participant self-assessment hair loss against that determined by an independent trained observer in their research clinic. Specifically, the self-assessed rating of score I in nine subjects was concurred by the trained observer in all but one individual who received a score of II ($p = 0.317$, Wilcoxon matched pairs signed rank test), whereas no discrepancies with observer's scores were detected in five individuals with self-assessed scores ranging from III to VII (Ellis *et al*, 1998).

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Address correspondence and reprint requests to: Dr Dale R. Nyholt, Queensland Institute of Medical Research, Post Office Royal Brisbane Hospital, Brisbane QLD 4029, Australia. Email: daleN@qimr.edu.au

Electronic Database Information: accession number and URL for data in this article are as follows: Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/(for MPB (MIM 109200), benign prostatic hyperplasia (MIM 600082), obesity (MIM 601665), hypertension (MIM 145500), and prostate cancer (MIM 176807)).

Data collected from 476 MZ and 408 DZ male pairs, plus 143 MZ and 154 DZ male individual twins (mean ages for the MZ and DZ twins were 30.3 and 30.5 y, respectively) were analyzed using structural equation modeling, to estimate parameters of a model that include additive genetic effects (A), nonadditive genetic effects (i.e., dominance or epistasis) (D), shared or family environment (C), and random or unique environment (E) (Neale and Cardon, 1992). In addition to the 12 Hamilton–Norwood categories, scoring individuals who answered "no" to the question "have you experienced hair loss?", as zero, resulted in a 13-point scale.

A major goal of the genetic analysis was to test the multiple threshold model (Reich *et al*, 1972; Kendler, 1993), which posits that different types of hair loss reflect different levels of severity on a single dimension, rather than distinct etiologies. These thresholds can be regarded as the z-value of the normal distribution that divides the area under the curve in such a way that it gives the right proportion of individuals in each (hair loss) group, thus reflecting the prevalence of each group (Neale and Cardon, 1992). For each of the two zygosity groups, the fit of a multiple threshold model was tested by calculating the polychoric correlation for the Hamilton–Norwood hair loss gradings, using POLYCORR (http://ourworld.compuserve.com/homepages/jsuebersax/xpc.htm) or PRELIS 2.30 (Jöreskog and Sörbom, 1999). The polychoric correlation, also termed the "correlation of liability", assumes that underlying the observed polychotomous distribution of hair loss status there exists a continuous, normally distributed latent liability (Kendler, 1993). A χ^2 goodness-of-fit test is used to test whether the multiple threshold model provides a good fit to the observed data. Calculation of 95% CI for the polychoric correlations, the comparison of threshold values within twin pairs and across zygosity groups, and genetic model fitting by maximum likelihood univariate analysis of raw data were performed using the Mx program (Neale *et al*, 1999).

Multiple threshold model tests performed on the 13 categories, assuming equal thresholds for twin 1 and twin 2, indicated no significant departure from normality in either MZ ($\chi^2_{155} = 117.94$, $p = 0.99$) or DZ twins ($\chi^2_{155} = 118.47$, $p = 0.99$), supporting a single liability dimension model of hair loss. As contingency tables using all 13 categories may be too sparse to yield a meaningful test of the multiple threshold model, however (e.g., the χ^2 statistic may not be asymptotically distributed), the MZ and DZ data were combined and the 13 score categories were collapsed into the following eight groups: group 1 (0, I, II, IIa; representing nonbaldness); group 2 (III); group 3 (IIIa); group 4 (IIIv, IV); group 5 (IVa); group 6 (V); group 7 (Va), and group 8 (VI, VII). Groups 2 to 8 represent significant cosmetic hair loss (Norwood, 1975), while maximizing counts for vertex and recessive hair loss. Multiple threshold model tests performed on both the full 8×8 table and after combining frequencies in the two off-diagonal quadrants, also indicated no significant departure from normality ($\chi^2_{48} = 55.47$, $p = 0.21$ and $\chi^2_{18} = 19.58$, $p = 0.36$, respectively). These results strongly support a single liability dimension model of hair loss, with frontal recession not etiologically distinct from vertex balding.

Subsequently, a single liability dimension-threshold model was applied to our hair loss data, using the full distribution of ordered hair loss scores (0–I–II–IIa–III–IIIa–IIIv–IV–IVa–V–Va–VI–VII) as an ordered sequence reflecting the severity of hair loss (see

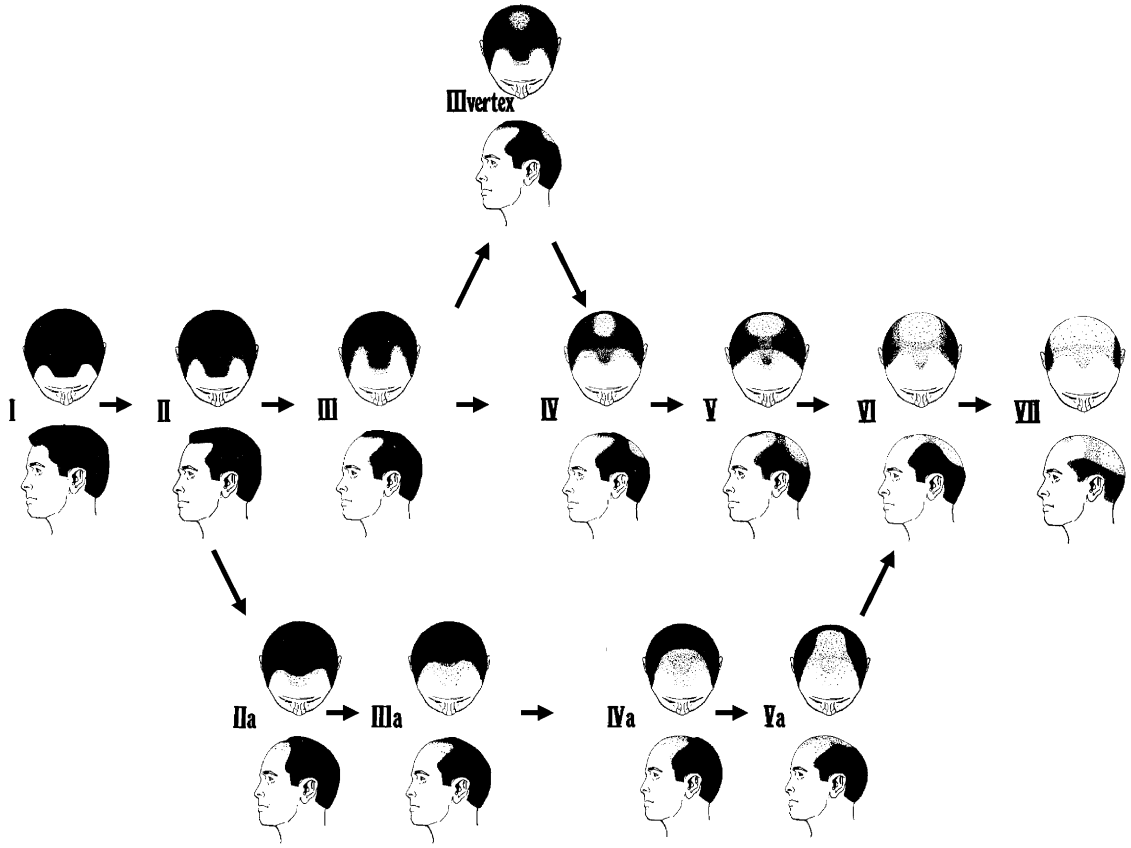

Figure 1. Hamilton–Norwood standards for classification of the most common types of MBP. Adapted from Norwood (1975). Types I, II, III, IV, V, VI, and VII represent the most common forms of MPB. Type IIIv has no more front temporal hair loss than type III, but has considerable hair loss at the vertex. Type A variants (IIa, IIIa, Iva, and Va) have hair loss restricted to the anterior region, which eventually recedes to equivalence with type VI (Norwood, 1975). Frequencies in our sample (2029 males aged 25–36 y) are: zero hair loss (61.2%), I (6.5%), II (14.2%), IIa (2.9%), III (4.3%), IIIa (1.5%), IIIv (3.8%), IV (1.6%), IVa (1.0%), V (0.8%), Va (1.1%), VI (0.4%), and VII (0.5%).

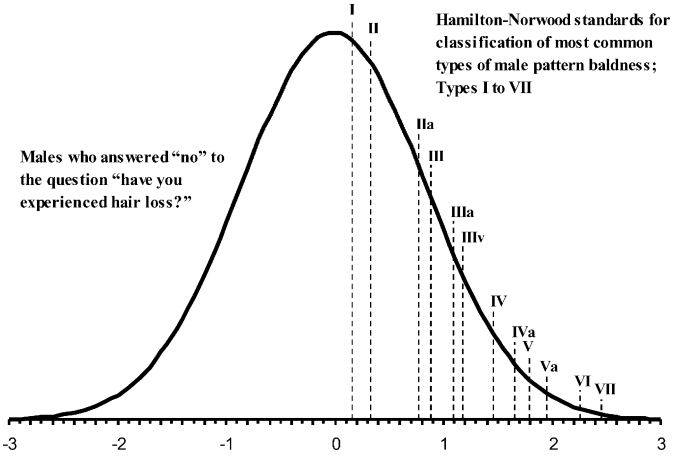

Figure 2. The multiple threshold model for the level of severity of hair loss for the best fitting AE model.

Fig 2). No significant differences in threshold liability distributions were observed within twin pairs and across zygosity groups. The age corrected maximum likelihood (ML) twin pair polychoric correlation for hair loss gradings in MZ twin pairs ($r = 0.81$; 95% CI: 0.77–0.85) was over twice as large as the DZ correlation ($r = 0.39$; 95% CI: 0.28–0.49), indicating a strong genetic effect. Furthermore, genetic model fitting by ML univariate analysis of raw data using Mx (Neale *et al*, 1999) (**Table I**), indicated that an additive genetic and nonshared environmental (AE) model best explained individual differences in MPB, and that 81% of the total variance could be attributed to additive genetic effects (i.e., 81% heritability, 95% CI: 77–85%).

Given the differences between some of the Hamilton–Norwood gradings are quite subtle, we re-analyzed our data using more clear-cut (dichotomous) categories of hair loss. For these analyses, males with gradings of III, IIIa, IIIv, IV, IVa, V, Va, VI, or VII were classified as bald, whereas males with gradings of 0, I, II, or IIa were classified as nonbald. Analogous to the previous genetic analyses, an AE model best explained individual differences in MPB, with 80% of the total variance attributed to additive genetic effects (95% CI: 70–87%). Furthermore, the AE model best explained individual differences in MPB for dichotomized clear-cut vertex balding (0, I, or II vs. IIIv, IV, V, VI, or VII) and recessive balding (0, I, or II vs. IIIa, IVa, or Va) producing heritability estimates of 89% (95% CI: 75–95%) and 96% (95% CI: 87–99%), respectively. As predicted under the multiple threshold model, and reflected in their overlapping confidence intervals, the use of different grouping thresholds/schemes does not produce significantly different heritabilities.

Surprisingly, there is only one known extensive family study on androgenetic alopecia published (Osborn, 1916). This study of hair growth patterns in 22 families concluded that common baldness is an autosomal dominant phenotype in men and an autosomal recessive phenotype in women. Owing to a lack of details regarding examination methods and the practice of omitting symptom-free women in some pedigrees, however, the validity of these results remain controversial. Additionally, although the results from the two other known twin studies produced concordance rates of 100% and 92.3% for MZ, and 50% and 68.7% for DZ twins, they are far too small—including only three MZ and

Table I. Genetic model fitting results using maximum likelihood raw data methods

					Goodness of fit					
Model	A	C	D	E	−2LL	d.f.	Δ-2LL	Δdf	p	vs. Model
ADE	0.75		0.06	0.19	5485.58	2013				
ACE	0.81	0.00		0.19	5485.68	2013				
AE[a]	0.81			0.19	5485.68	2014	0.09	1	0.76	ADE
CE		0.62		0.38	5552.84	2014	67.16	1	<0.001	ACE

Liability thresholds, computed using PRELIS 2.30 (Jöreskog and Sörbom, 1999), were utilized as starting values for the maximum likelihood univariate genetic analysis of raw data, performed using the Mx program (Neale *et al*, 1999). The correlation between age and baldness was accounted for by simultaneously estimating and applying a single age displacement (normalized regression coefficient) ($\beta = -0.06$) to the threshold distribution. First, a fully "saturated" model (ADE or ACE) was tested to evaluate the statistical properties of the data, then the effect of dropping one of the parameters (A, C, D, or E) was examined by testing the respective difference (Δ-2LL) for statistical significance.

[a]The AE model was found to provide the most parsimonious fit to the data.

eight DZ male pairs (Niermann, 1964; Kuster and Happle, 1984), and 65 MZ (42 male, 23 female) and 16 DZ (14 male, two female) pairs (Hayakawa *et al*, 1992), respectively—to permit reliable conclusions.

Therefore, our results represent one of the first large-scale studies on the heritability of MBP and indicate that additive genetic effects play a major part in the progression of common hair loss. Moreover, a recent study by Ellis *et al* (2001), which tested polymorphisms in the androgen receptor (*AR*) gene, found a *Stu*I restriction site in 98.1% of 54 young (18–30 y) bald men ($p = 0.0005$) and in 92.3% of 392 older (>50 y) bald men ($p = 0.000004$) compared with 76.6% of 107 nonbald (>50 y) men, suggesting that a polymorphism in or near *AR* (and in linkage disequilibrium with the *AR Stu*I restriction site) is a contributing, but not sufficient, component of the genetic predisposition to MPB. Moreover, the *AR* gene is on chromosome Xq11.2–q12 and therefore could not explain the similar hair loss patterns shared between father and sons, as observed in an earlier study on the same population, where 32 of 54 bald cases (59.3%) had fathers with a greater degree of baldness, and only one of 65 sons of 50 nonbald controls had type III baldness or greater (Ellis *et al*, 1998).

Hair loss similarities between father and son have also been observed in a study on the frequency of MPB in brothers of men having prematurely bald fathers (66%) compared with brothers of men with unaffected fathers (46%; Harris, 1946; Kuster and Happle, 1984). Further evidence against a single and/or X-linked gene of major effect comes from a study by Smith and Wells (1964), which observed hair loss in only 33% of the fathers of 18 women suffering from severe pattern baldness (Kuster and Happle, 1984). Additionally, a study examining 410 men with premature baldness found evidence of a genetic influence from the father's side in 236 cases (Galewsky, 1932; Jackson, 1932; Kuster and Happle, 1984). Hence, other (autosomal) genes, possibly of large effect, remain to be found.

It is worth noting that these heritabilities are based on a relatively young population—ranging in age from 25 to 36 with a mean of 30 y. As some of the nonbald subjects will inevitably develop balding—with the rate of baldness known to increase steadily with age—it is possible that heritability (A) will differ with age. For example, through the age-dependent expression of genes, and/or a change in the body's resilience to the major effects of a genetic influence in early phases of life. Also, the accumulation of environmental influences (E) may play a larger part in older ages. Twin studies in older cohorts are required to investigate these possibilities.

The negative psychosocial effects associated with male hair loss include decreased self-esteem, dissatisfaction with body image or appearance, self-consciousness, perception of aging, and often emotional stress. Furthermore, these effects tend to be more pronounced in younger men (Girman *et al*, 1998). Certainly, MPB in itself has a considerable effect on the quality of life for many men. Because it is a clearly observable trait, however, which generally precedes the diagnosis of benign prostatic hyperplasia and clinical prostate cancer by decades (Hawk *et al*, 2000), genes influencing MPB may prove valuable in determining susceptibility to life-threatening prostatic disorders. Moreover, genes influencing MPB, may lead to the identification of novel mechanisms, which may influence cardiovascular disease and/or insulin resistance.

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Dale R. Nyholt, Nathan A. Gillespie, Andrew C. Heath,* and Nicholas G. Martin
Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, Brisbane, Queensland, Australia; *Department of Psychiatry, Washington University School of Medicine, St Louis, Missouri, USA

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